Updates in the Treatment of Aggressive Lymphoma DLBCL

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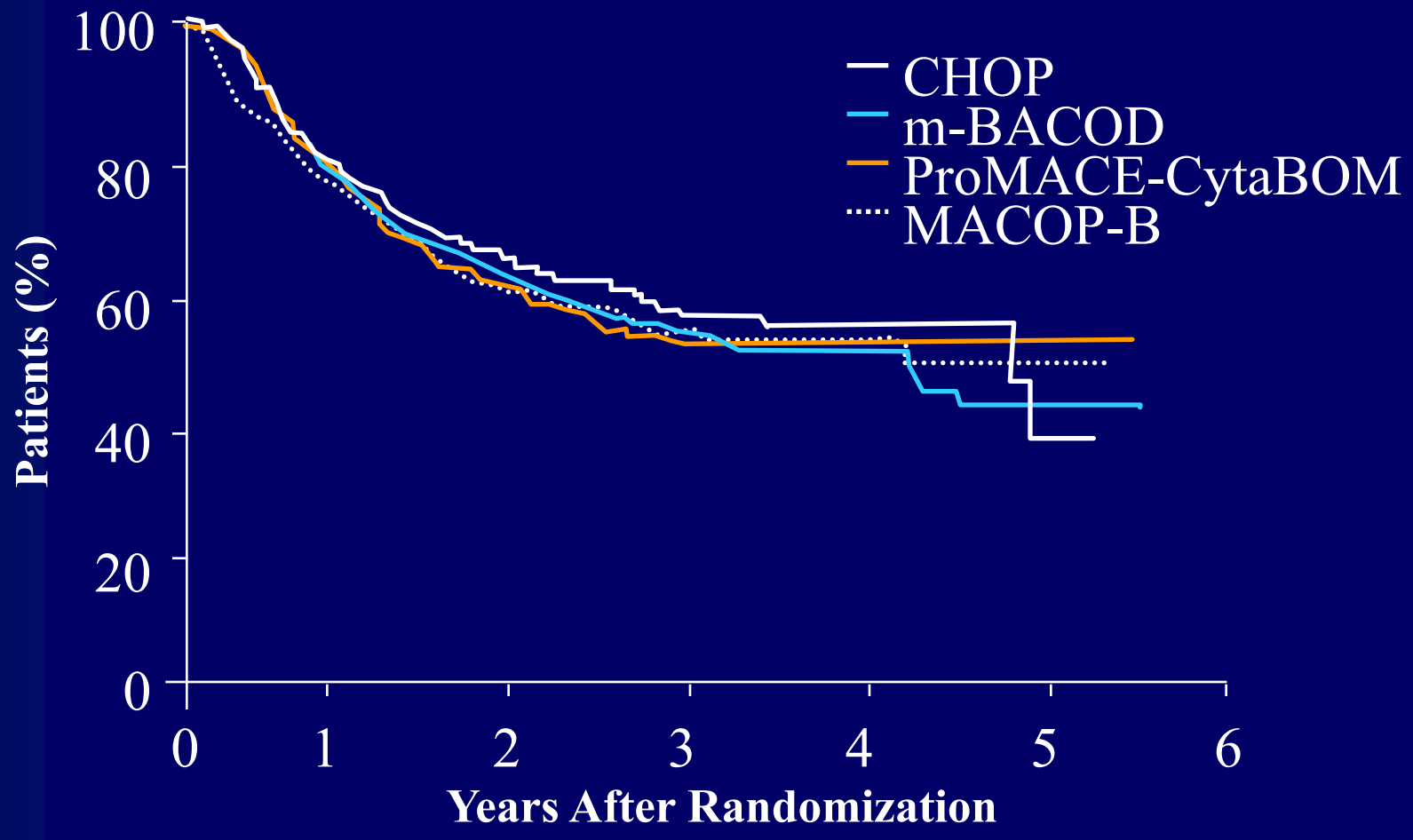
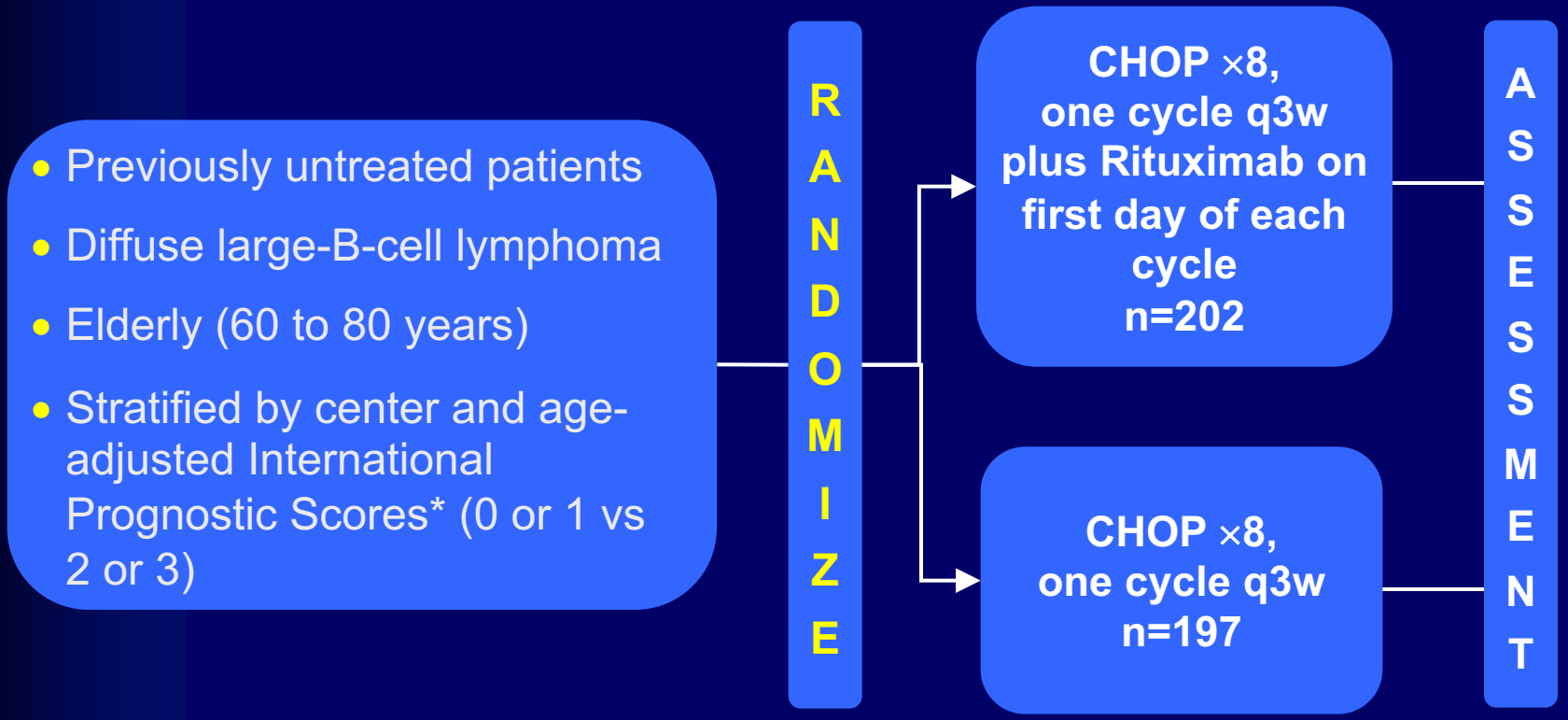
National High Priority Lymphoma Study: Progression-Free Survival



Adapted from Fisher. *N Engl J Med.* 1993;328:1002.

Advanced Stage (III/IV) DLBCL
LNH 98-5 Trial (Gela Study)



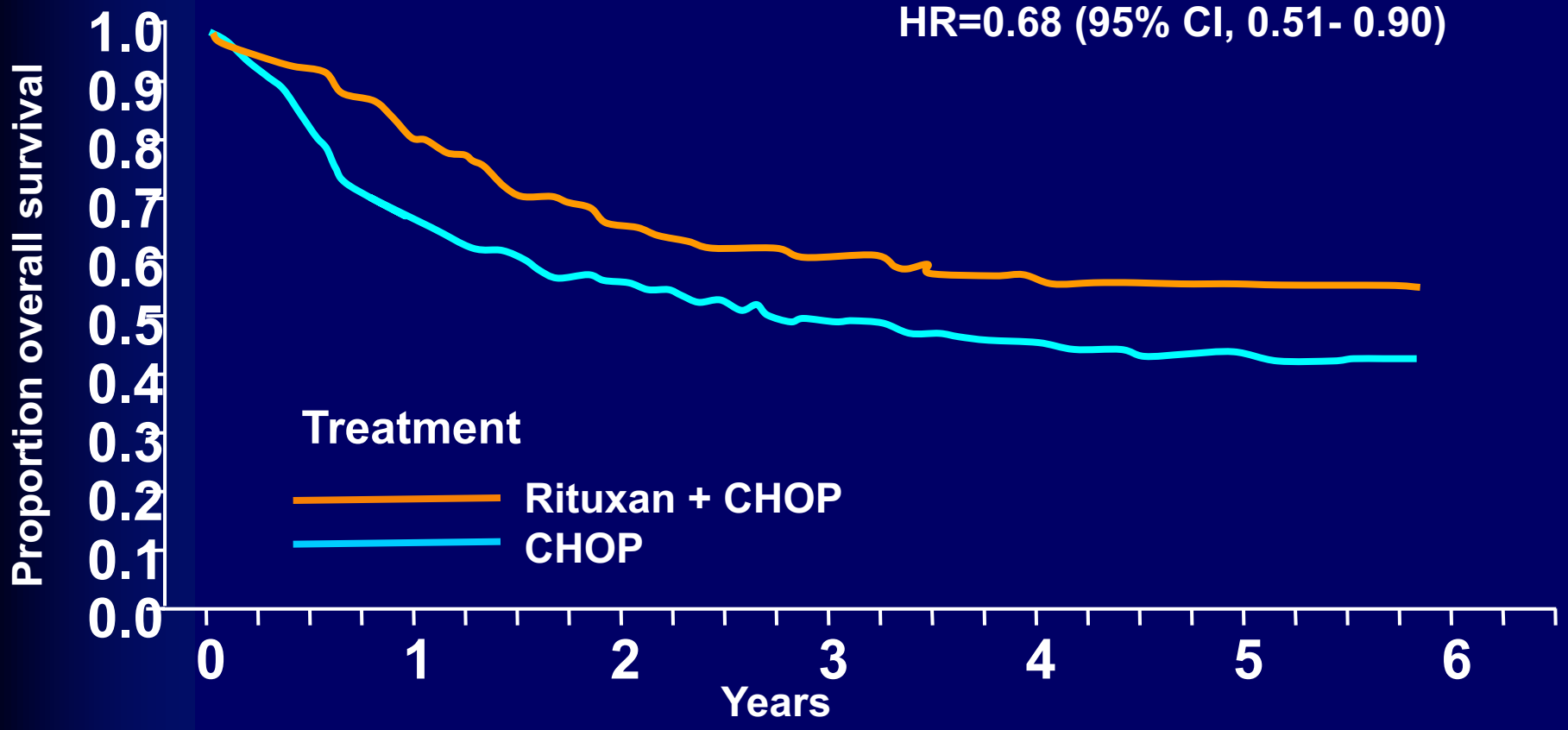
- Primary endpoint: event-free survival
- Secondary endpoints: overall survival, response rates, and toxicity

Events were defined as disease progression or relapse, institution of a new anticancer treatment, or death from any cause without progression.

*Based on disease stage, PS, and LDH.

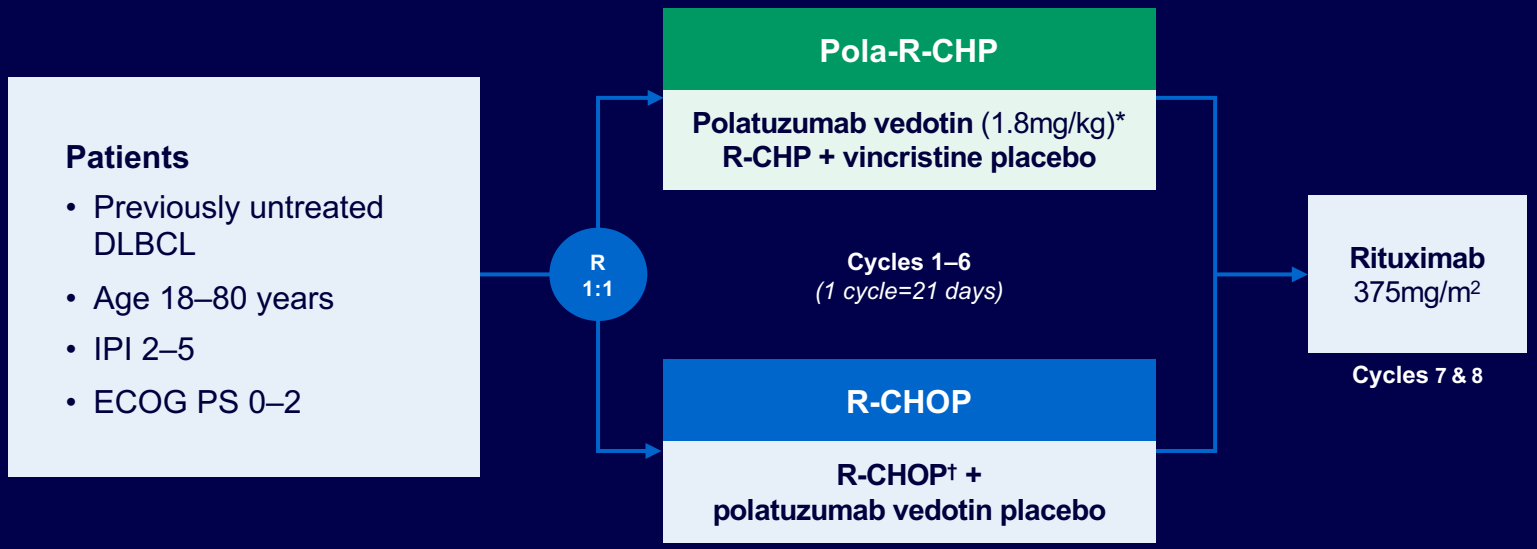
Coiffier et al. *N Engl J Med*. 2002;346:235.

LNH 98-5 Trial: Overall Survival
Median 5-Year Follow-up



Coiffier et al. *N Engl J Med*. 2002;346:235.

Phase 3 POLARIX Study: Polatuzumab Vedotin + R-CHP Versus R-CHOP for Newly Diagnosed DLBCL—Study Design



Stratification factors

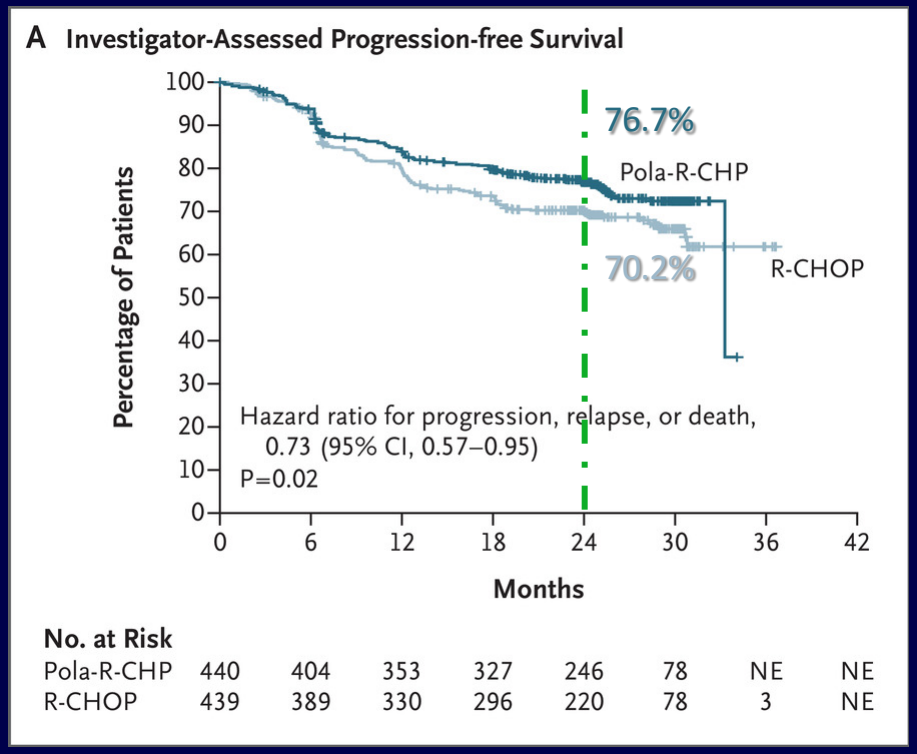
- IPI score (2 vs 3–5)
- Bulky disease (<7.5 vs ≥7.5cm)
- Geographic region (Western Europe, US, Canada, & Australia vs Asia vs rest of world)

- Primary endpoint: PFS (INV)
- Secondary endpoints: EFS, CR at EOT, DFS, OS, safety

Median follow up, 28.2 mo; data cut off: 28 JUN 2021.

Tilly H, et al. *N Engl J Med*. 14 Dec 2021. Tilly H, et al. ASH 2021 LBA1.

Phase 3 POLARIX Study: PFS (INV)—Primary Endpoint

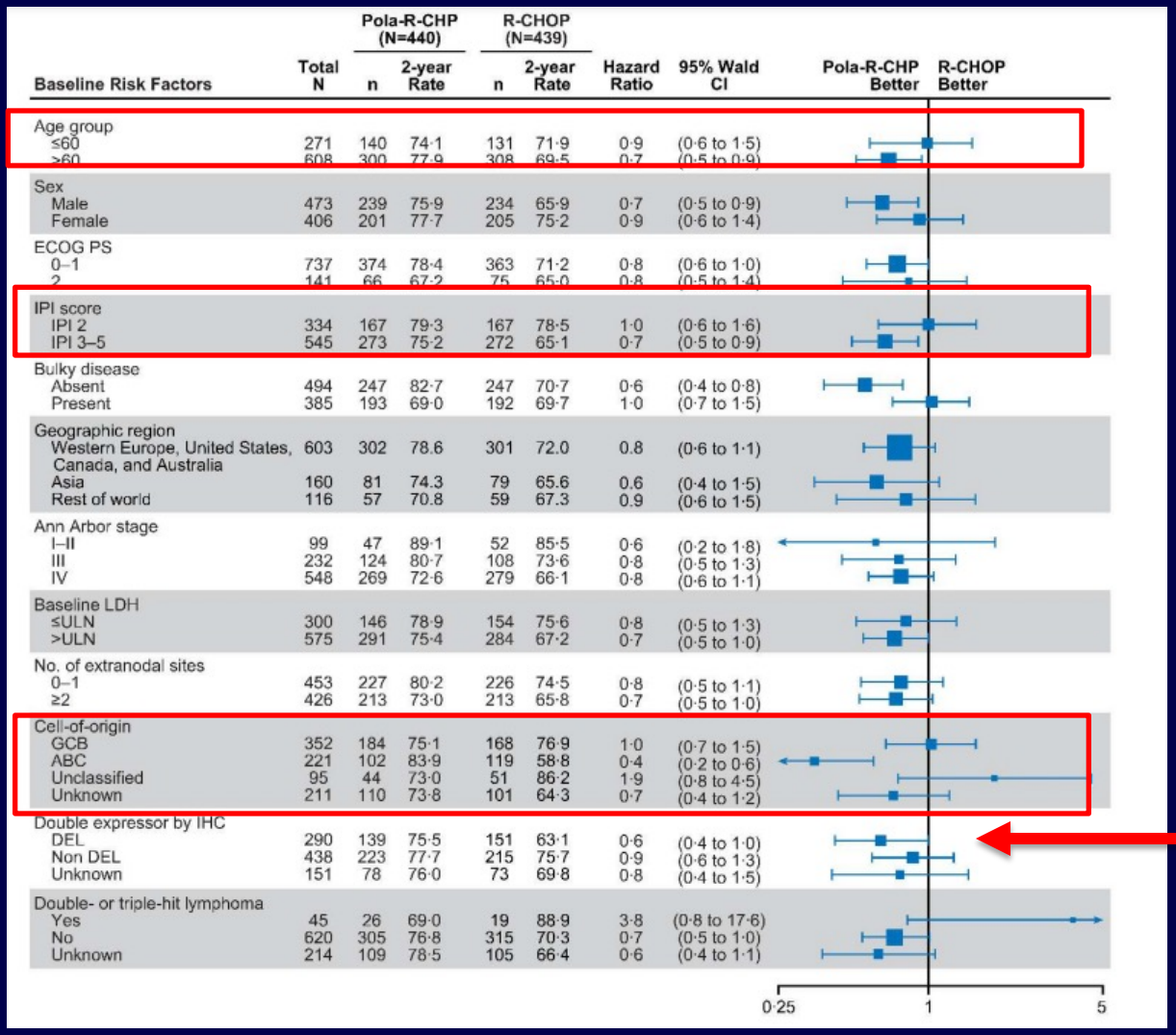


- 27% reduction in risk of progression, relapse or death with Pola-R-CHP

Median follow up, 28.2 mo; data cut off: 28 JUN 2021.
Tilly H, et al. *N Engl J Med*. 14 Dec 2021. Tilly H, et al. ASH 2021 LBA1.

Phase 3 POLARIX Study: PFS (INV) by Subgroup

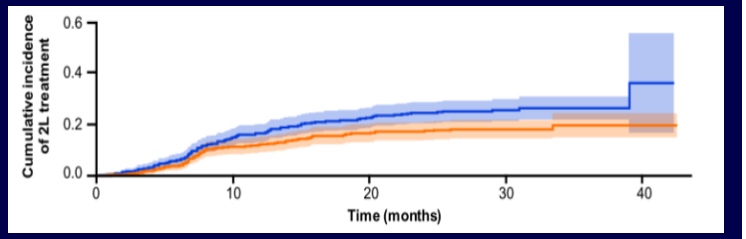
Exploratory Analysis



Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)

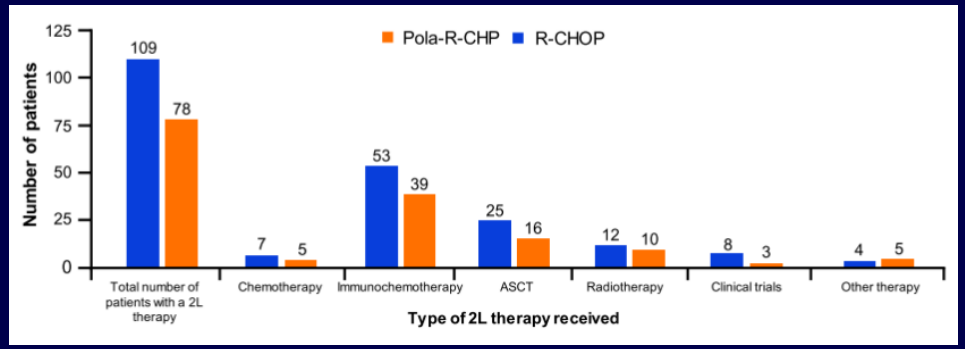
Analyses From the POLARIX Phase 3 Trial of Pola-R-CHP vs R-CHOP in Patients With 1L DLBCL: Impact on 2L Therapy Risk and Selection

Cumulative Incidence of 2L Therapy



- Patients treated with Pola-R-CHP were 34% less likely to require 2L therapy vs R-CHOP (HR: 0.66; 95% CI: 0.48-0.88)

Type of 2L Therapy by 1L Therapy Received



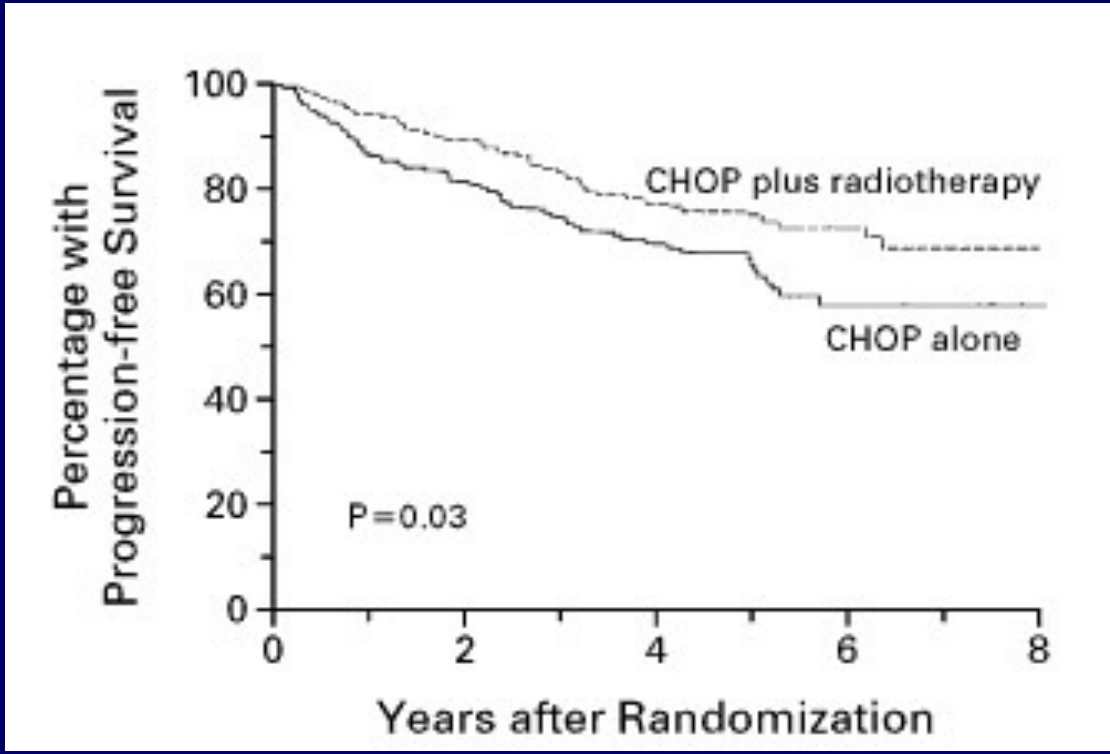
- Fewer patients receiving 2L therapy after Pola-R-CHP than after R-CHOP
- The distribution of 2L therapy types was similar, suggesting that Pola-R-CHP does not impact 2L therapy for R/R DLBCL
- Replacing R-CHOP with Pola-R-CHP for 1L therapy could reduce the need for 2L therapy by 27% over a 10-year period

Boissard F, et al. ASH 2022. Abstract 2958.

Treatment of Early Stage DLBCL

Early Stage (I/II) DLBCL

Progression-free Survival of 201 Patients Receiving Eight Cycles of CHOP Alone and 200 Patients Receiving Three Cycles of CHOP plus Radiotherapy.

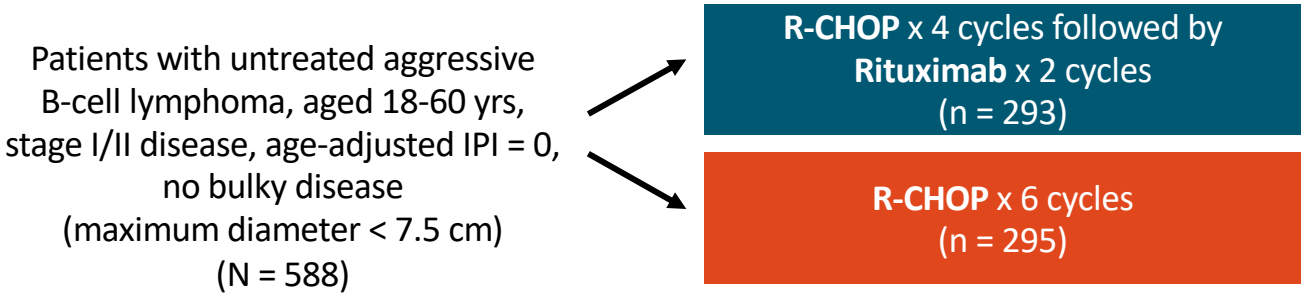


Miller TP et al. N Engl J Med 1998;339:21-26.

The NEW ENGLAND JOURNAL of MEDICINE

FLYER: Study Design

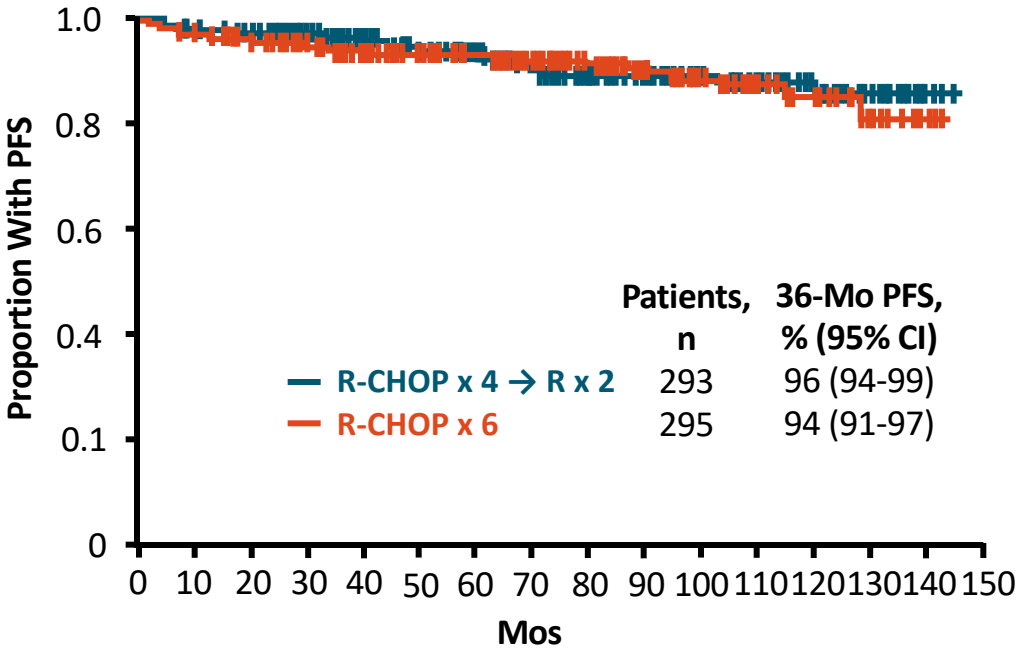
- International, randomized phase III noninferiority trial



- Primary endpoint: PFS, 3-yr PFS rate
  - Assumed 3-yr PFS rate of 93% with R-CHOP x 6
  - Difference up to -5.5% allowed with R-CHOP x 4 → R x 2 while still proving noninferiority with 80% power and 1-sided $\alpha = 0.05$ (planned sample size: N = 592, assuming 10% loss yields final N = 532)
- Other endpoints: response, EFS, OS, safety

Poeschel. ASH 2018. Abstr 781.

FLYER: PFS (Primary Endpoint)



- After median f/u of 66 mos, PFS noninferior with R-CHOP x 4 → R x 2 vs R-CHOP x 6

Poeschel. ASH 2018. Abstr 781. Reproduced with permission.

Salvage Therapy for Relapsed or Refractory DLBCL

"Standard" Salvage Regimens for R/R DLBCL (Pre-Auto Transplant)

Table I. Salvage chemotherapy regimens in randomized studies for DLBCL [Gisselbrecht *et al*, 2010 (CORAL study); Crump *et al*, *2014* (LY.12 study); van Imhoff *et al*, 2017 (ORCHARRD study)].

Salvage induction	N	RR	Transplant rate	PFS
R-ICE	202	64%	51%	3-year: 31%
R-DHAP (CORAL)	194	63%	55%	3-year: 42%
(R)-DHAP (LY12)	304	45%	49%	3-year: 28%
(R)-GDP	306	44%	52%	3-year: 28%
R-DHAP (ORCHARRD)	223	42%	37%	2-year: 26%
O-DHAP (ORCHARRD)	222	38%	33%	2-year: 24%

(R)-GDP, (rituximab)-gemcitabine, dexamethasone, cisplatinum; DLBCL, diffuse large B cell lymphoma; O-DHAP, Ofatumumab- dexamethasone, cytarabine, cisplatin; PFS, progression-free survival; R-DHAP, rituximab-dexamethasone, cytarabine, cisplatin; R-ICE, rituximab-ifosfamide, etoposide, carboplatin; RR, relative risk.

Gisselbrect C et al, BJH 2018

Salvage Regimens for R/R DLBCL

Table II. Overall response rate of new selected single agents in DLBCL patients.

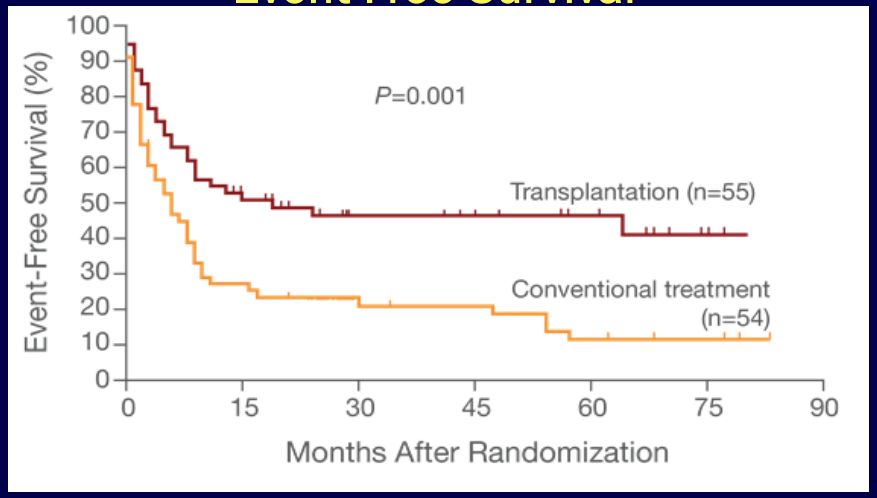
Agent	Target	Status	ORR	DLBCL subtype	References
Ibrutinib	BTK	Phase I/ II	37%	ABC	Wilson *et al* (2015)
Fostamatinib	SYK	Phase II	3%	DLBCL	Flinn *et al* (2016)
			22%		Friedberg *et al* (2010)
Lenalidomide	Immunomodulator	Phase II	42%	DLBCL	Zinzani *et al* (2015)
			52%	ABC	Hernandez-Ilizaliturri *et al* (2011)
Bortezomid + chemotherapy	NF-κB	Phase II	83%	ABC	Dunleavy *et al* (2009)
Tazemetostat	EZH2	Phase II	60%	DLBCL	Italiano *et al* (2018)
Everolimus	mTOR	Phase II	30%	GCB	Witzig *et al* (2011)
Temsirolimus	mTOR	Phase II	28%	DLBCL	Smith *et al* (2010)
CUDC 907	PI3Kδ + HDAC	Phase II	37%	GCB/*MYC*	Oki *et al* (2017)
Bendamustine	Nitrogen mustard/ purine-like	Phase II	44%	DLBCL	Weidmann *et al* (2002)
Obinutuzumab	CD20	Phase II	32%	DLBCL	Morschhauser *et al* (2013)
MOR00208	CD19	Phase II	29%	DLBCL	Jurczak *et al* (2018)
Blinatumumab	B-specific CD19/CD3	Phase II	43%	DLBCL	Viardot *et al* (2016)
Polatuzumab vedotin	CD79b	Phase I	25%	DLBCL	Palanca-Wessels *et al* (2015)
Nivolumab	Anti-PD1	Phase I	36%	DLBCL	Lesokhin *et al* (2016)

ABC, activated B cell; DLBCL, diffuse large B cell lymphoma; GCB, germinal centre B cell; ORR, overall response rate.

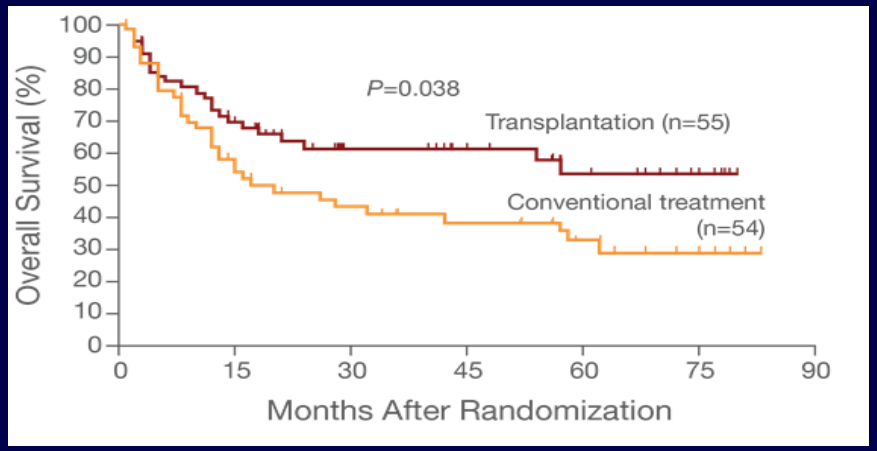
Gisselbrect C et al, BJH 2018

Standard of Care for Chemosensitive R/R DLBCL Is ASCT

Event-Free Survival[1]



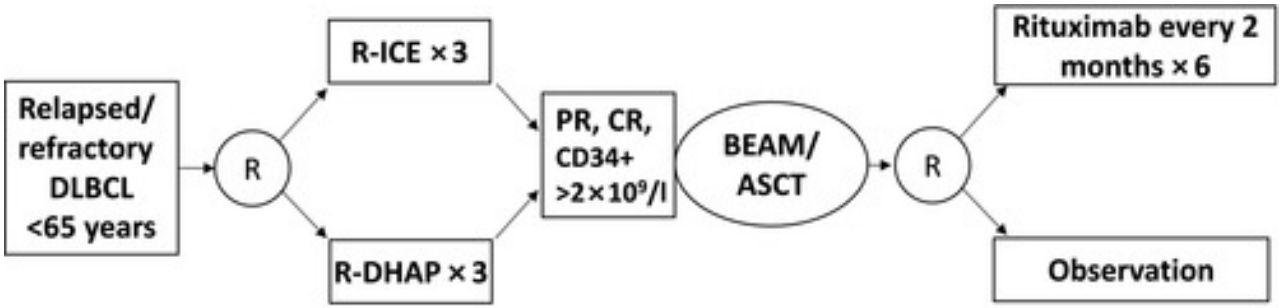
Overall Survival[1]

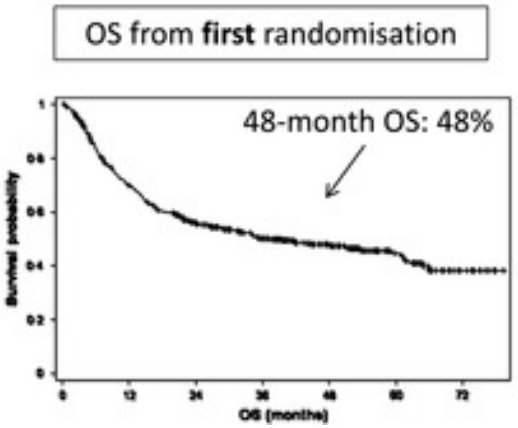


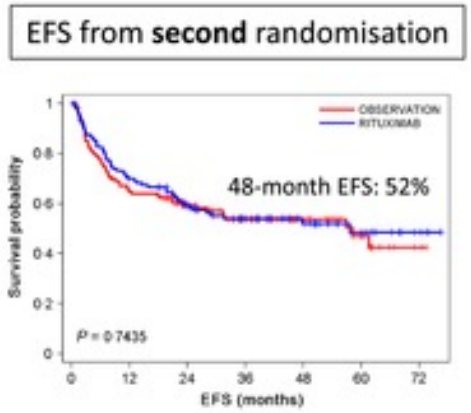
- 20% to 50% of patients will relapse or be refractory to R-CHOP, depending on IPI[2]
- 30% to 40% of patients will respond to salvage chemotherapy and proceed to ASCT[2]
  - Relative equivalency with intensive salvage regimens
- 50% will relapse after ASCT[2]

1. Philip T, et al. *N Engl J Med.* 1995;333(23):1540-1545. 2. Crump M, et al. *Blood*. 2017;130(16):1800-1808.

How I manage patients with relapsed/refractory diffuse large B cell lymphoma







Salvage autologous transplant remains the SOC for R/R Chemo sensitive DLBCL-

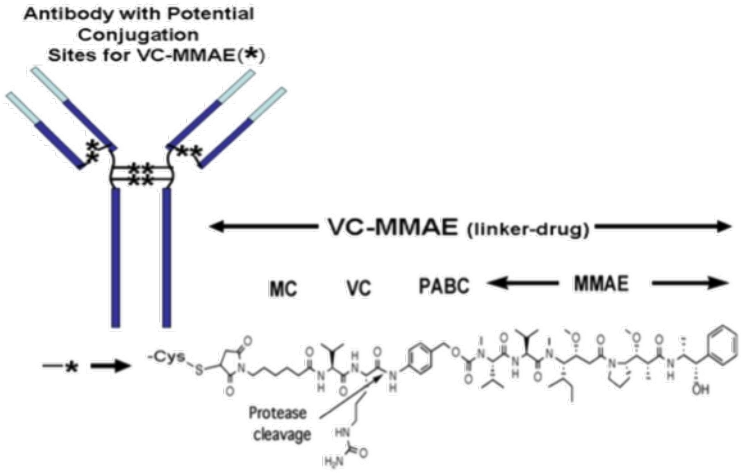
What about when patients are not chemosensitive or are primary refractory?

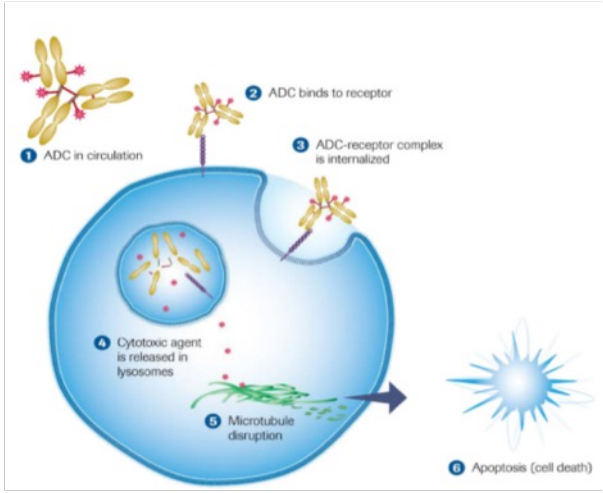
British Journal of Haematology, Volume: 182, Issue: 5, Pages: 633-643, First published: 29 May 2018, DOI: (10.1111/bjh.15412)

Newer *Targeted Agents for the Treatment of Relapsed DLBCL*

Polatuzumab vedotin

- Polatuzumab vedotin (pola) is an antibody drug conjugate (ADC) consisting of a potent microtubule inhibitor monomethyl auristatin E (MMAE) conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker

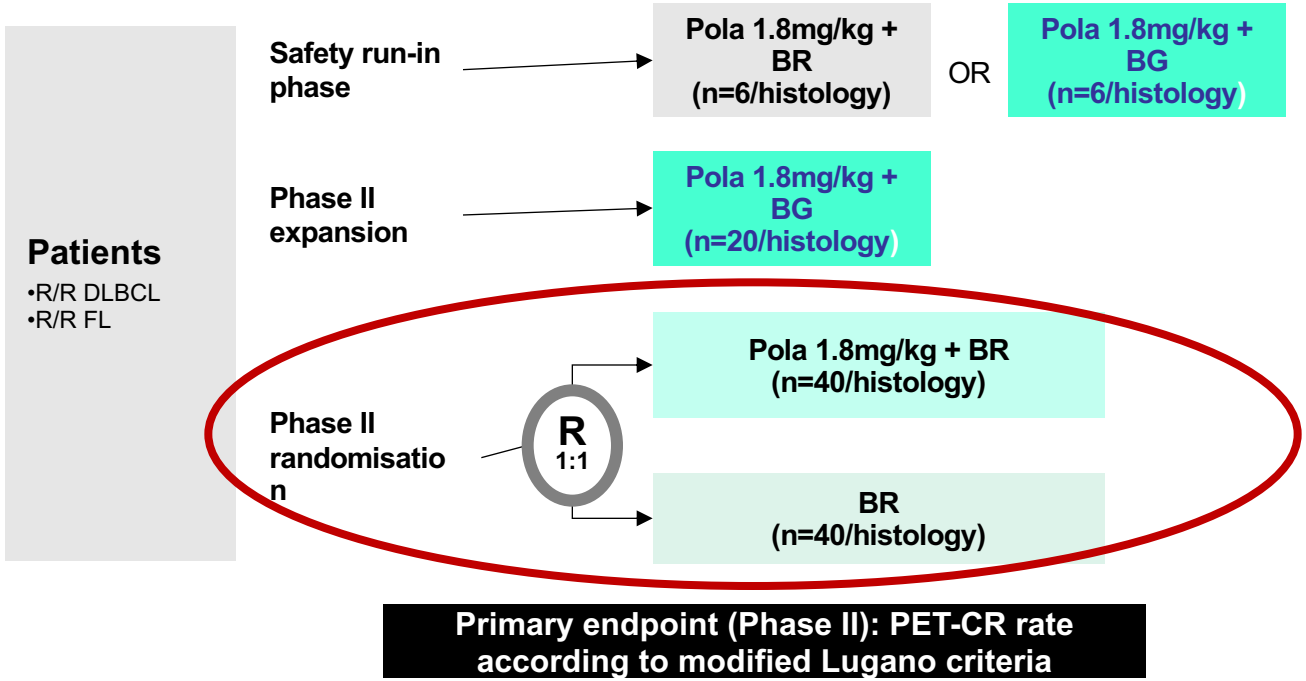




- Pola has demonstrated efficacy in R/R DLBCL in combination with rituximab[1,2]

Treatment	Best overall response
Pola +/- rituximab	51–56%[1,2]

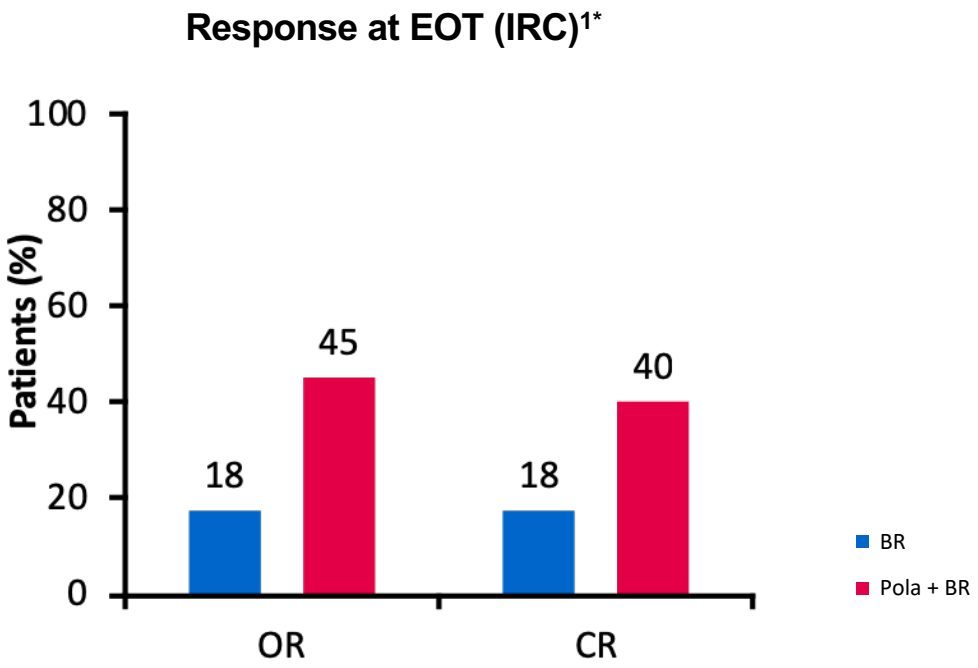
1. Palanca-Wessels A, et al. Lancet Oncol, 2015;16:704–15
2. Morschhauser F, et al. Lancet Hematology, 2019;6:e254 –65



BG, bendamustine and obinutuzumab; BR, bendamustine and rituximab; FL, follicular lymphoma; PET-CR, positron electron tomography–complete response; pola, polatuzumab vedotin; R, randomisation; R/R, relapsed/refractory

Sehn L, et al. Abstract #1683, ASH 2018

Polatuzumab vedotin added to bendamustine/ rituximab



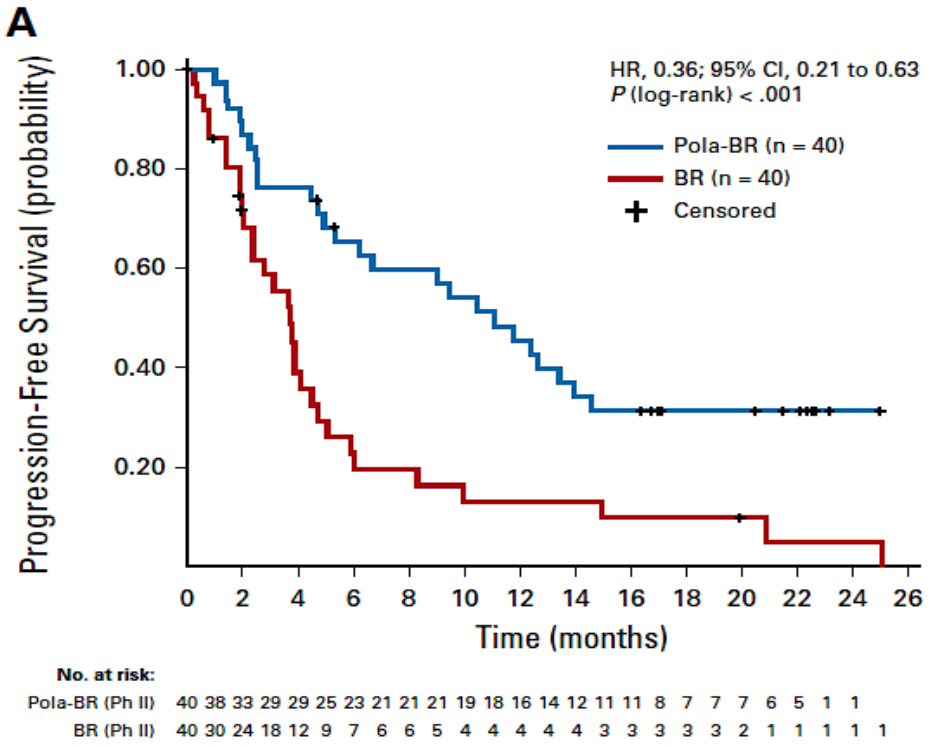
Seven patients have ongoing response durations of ≥20 months at data cut-off

1. Sehn L, et al. Abstract #1683, ASH 2018 | 2. Sehn L, et al. Abstract #7507. ASCO 2018

Data cut-off: 1. 30 April 2018, 2. May 2017
*Primary endpoint; PET-CR is assessed by modified Lugano criteria
BOR, best overall response; BR, bendamustine and rituximab; CR, complete response; EOT, end of treatment; INV, investigator; IRC, independent review committee; OR, objective response; pola, polatuzumab vedotin

Polatuzumab vedotin added to bendamustine/rituximab

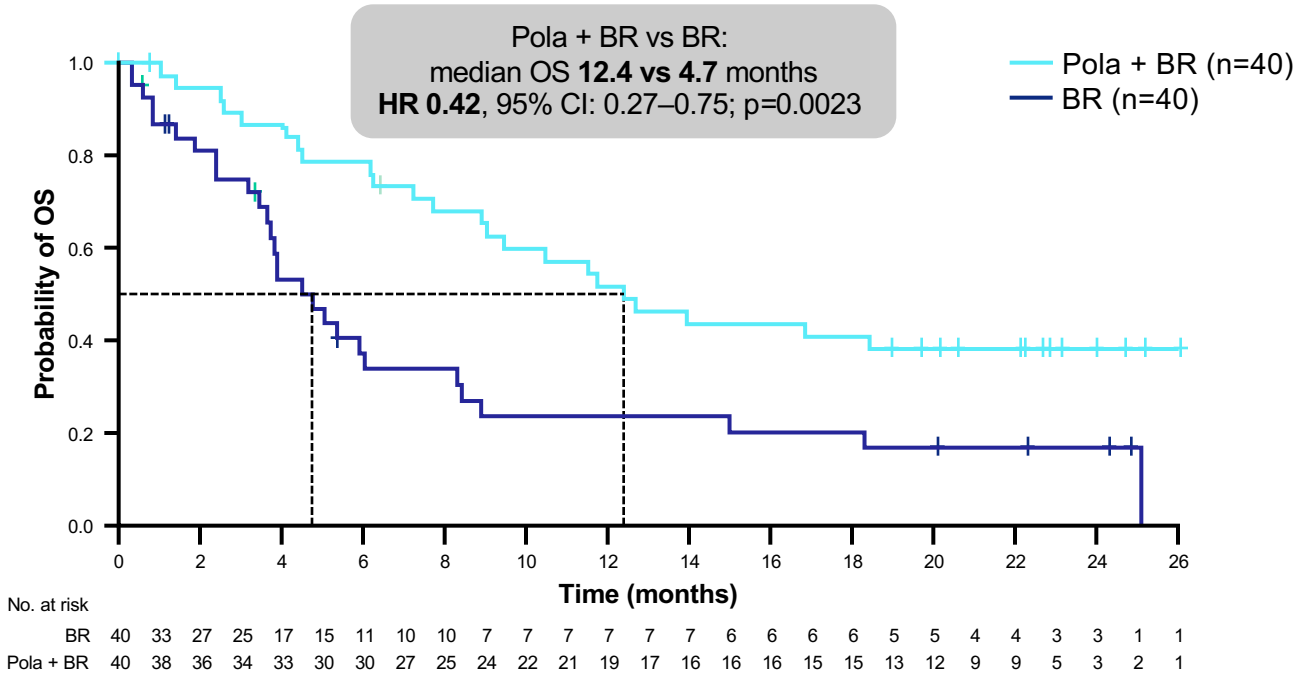
Progression Free Survival (IRC)



- Few patients with durable responses
- Toxicity: hematological, infectious, neurological

Sehn, JCO 2019

Overall Survival



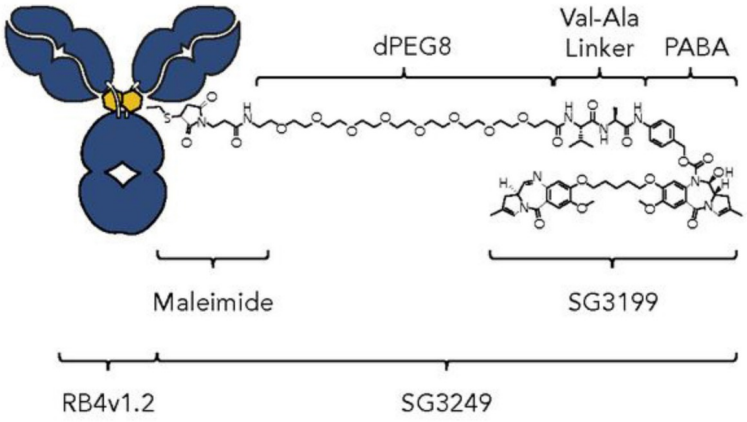
Median follow-up: 22.3 months

Sehn L, et al. Abstract #1683, ASH 2018

Data cut-off: 30 April 2018
BR, bendamustine and rituximab; pola, polatuzumab vedotin

Loncastuximab Tesirine

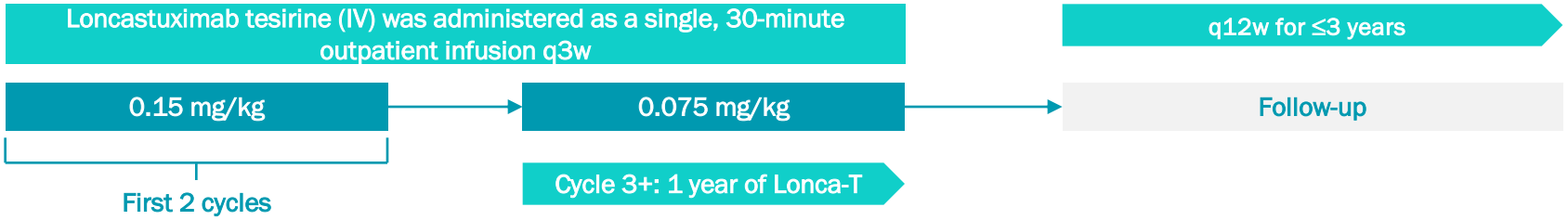
- Loncastuximab tesirine is an FDA-approved CD19-directed antibody-drug conjugate indicated for adults with R/R large B-cell lymphoma after ≥2 lines of systemic therapy, including patients with HGBCL[1]
- ADC delivering SG3199, a cytotoxic DNA minor groove interstrand cross-linking PBD dimer payload[1,2]
  - Anti-CD19
  - Payload is a PBD toxin
  - DNA cross-linking agent



1. Loncastuximab tesirine. Package insert. ADC Therapeutics, SA; 2021. **2.** Zammarchi F, et al. *Blood*. 2018;131(10):1094-1105.

LOTIS-2: Study Design

- Patients with R/R DLBCL for whom salvage chemotherapy/SCT is unsuccessful and who have a poor prognosis and limited treatment options[1,2]
- Loncastuximab tesirine comprises a humanized anti-CD19 antibody conjugated to a potent PBD dimer toxin[3]
- LOTIS-2 is a multicenter, open-label, single-arm, phase 2 study in patients aged ≥18 years with pathologically defined R/R DLBCL and ≥2 prior systemic treatments[4-6]
  - Included patients with high-risk characteristics such as double-hit, triple-hit, transformed, or primary refractory DLBCL[4]

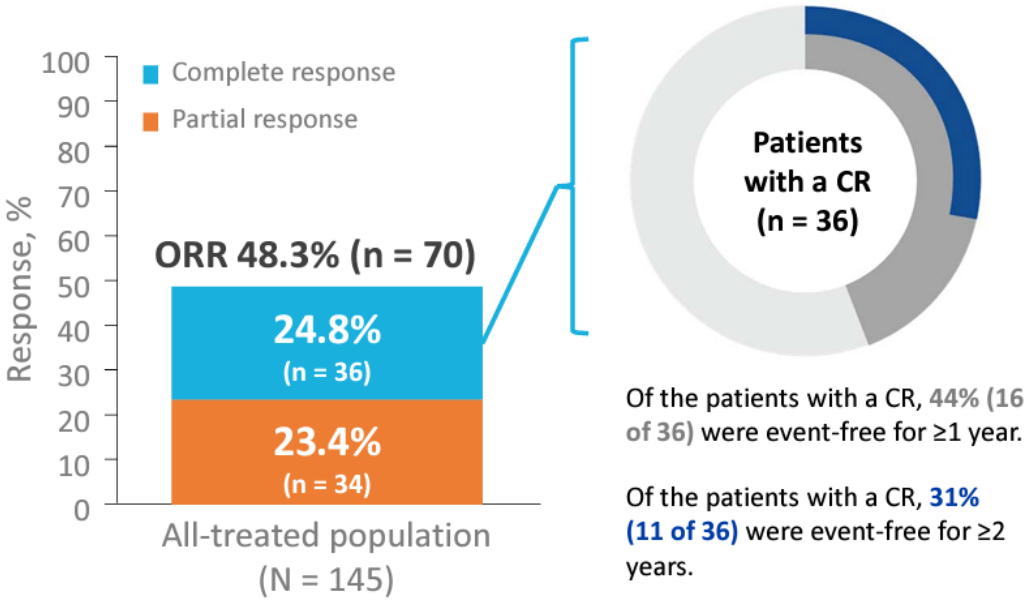


- Primary efficacy and safety data have been published (**≥6 months** since first dose)[4]
- Presented are updated results (**≥17 months** since first dose)

Study findings were previously presented as a poster at the International Conference on Malignant Lymphoma (ICML) Virtual Congress, June 18-22, 2021.

1. Crump M, et al. *Blood.* 2017;130(16):1800-1808. **2.** Gisselbrecht C, et al. *Br J Haematol.* 2018;182(5):633-643. **3.** Zammarchi F, et al. *Blood.* 2018;131(10):1094-1105. **4.** Caimi PF, et al. *Lancet Oncol.* 2021;22(6):790-800. **5.** Caimi PF, et al. ASH 2020. Abstract 1183. **6.** Caimi PF, et al. ASCO 2021. Abstract 7546. **7.** Caimi PF et al. ICML 2023. Abstract 137.

LOTIS-2: Efficacy Results – ORR and Long-Term Responses

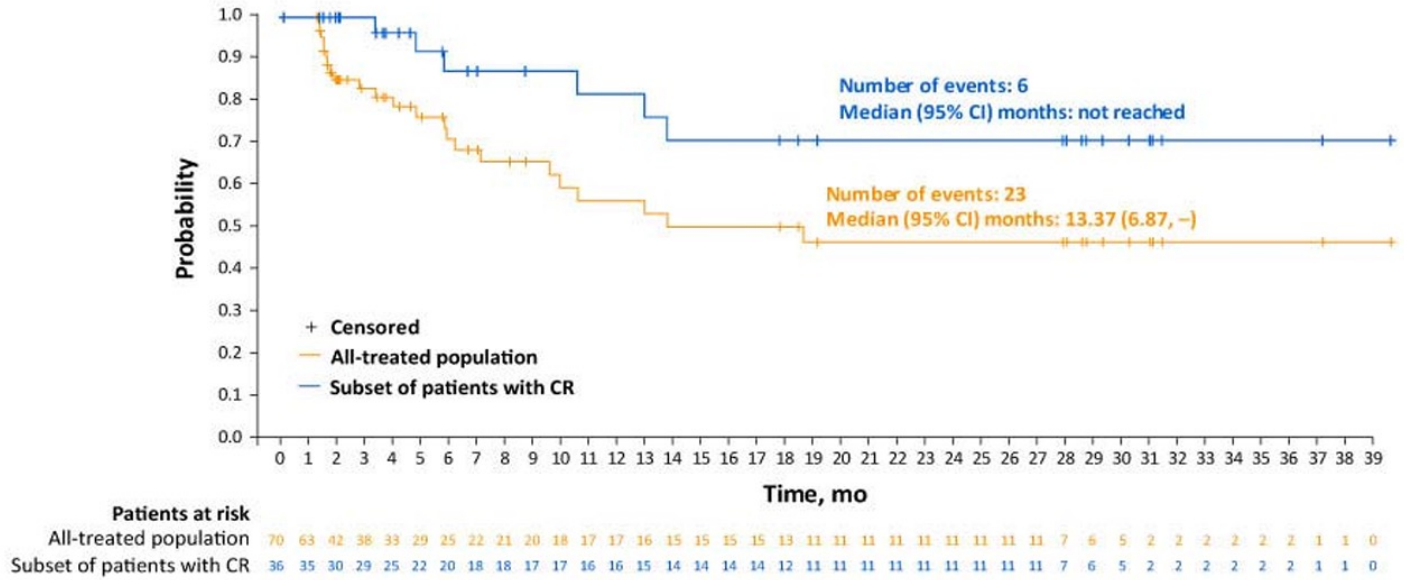


Median (range) number of treatment cycles	
All-treated population	3.0 (1-26)
Patients with a CR	8.0 (1-26)
Patients with a CR, event-free ≥1 year[a]	12.5 (1-26)
Patients with a CR, event-free ≥2 years[a]	13.0 (1-22)

Data cutoff: September 15, 2022. Median duration of follow-up was 7.8 months (range, 0.3-42.6 months) in the all-treated population and 35.0 months (range, 4.-42.6 months) in the patients with a CR.
aEvent-free is defined as no progressive disease or death starting from day 1 cycle 1 of loncastuximab tesirine treatment.
Caimi PF et al. ICML 2023. Abstract 137.

LOTIS-2: Efficacy Results – DOR

DOR in All-Treated Population and Patients with a CR



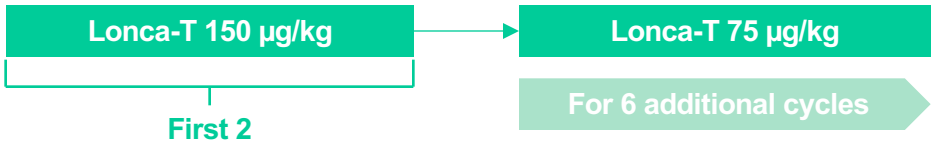
The median (range) time to response was 41 (35-247) days in the all-treated population and 42 (36-247) days for patients with a CR.

Data cutoff: September 15, 2022.
Caimi PF et al. ICML 2023. Abstract 137.

LOTIS-5: Initial Safety Run-in Results of Part 1

- LOTIS-5 is a phase 3, randomized, open-label, 2-part, 2-arm, multicenter study of Lonca-T + R in patients with R/R DLBCL with ≥1 previous therapy and unfit for SCT
- In part 1, 20 patients were enrolled in a nonrandomized safety run-in with Lonca-T + R to demonstrate the safety of the Lonca-T + R combination in patients

Nonrandomized Safety Run-in of IV Lonca-T + R q3w (Target N=20)



Response Rates by Central Review, n (%)	n=20
ORR	16 (80)
CR	10 (50)
PR	6 (30)

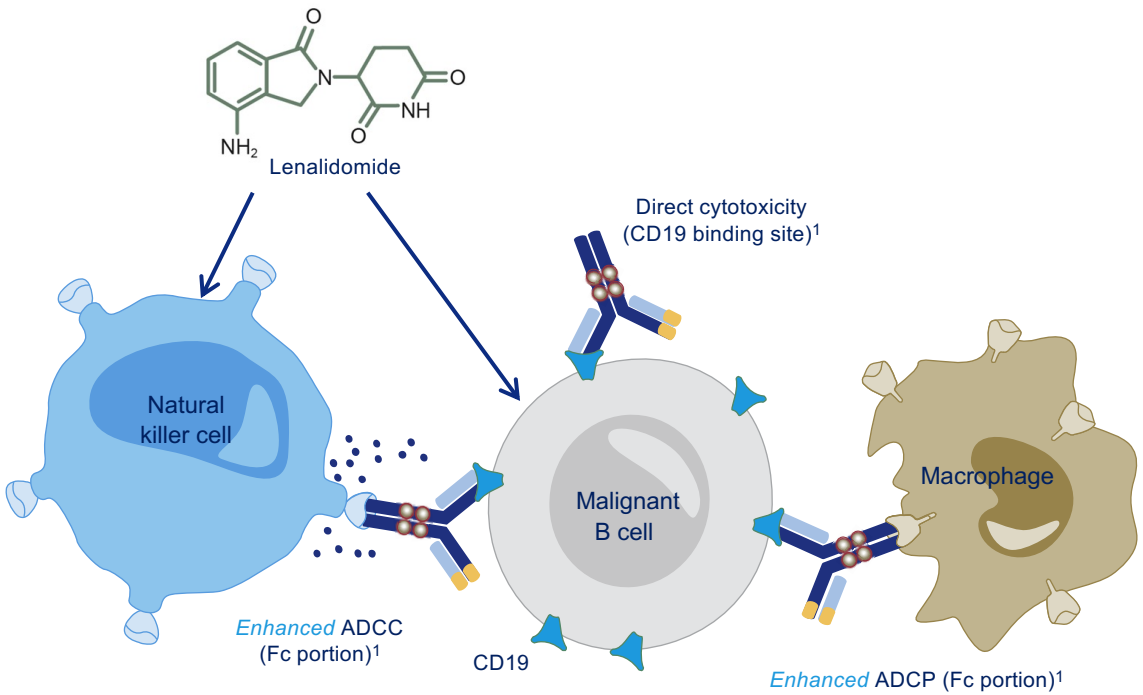
Efficacy in Patients With R/R DLBCL, n (%) [95% CI]	n=20
ORR	16 (80) [56.3-94.3]
CR	10 (50) [27.2-72.8]
PR	6 (30) [11.9-54.3]
Safety endpoints, n (%)	
Any grade TEAE	20 (100)
Rash	5 (25)
Increased GGT	5 (25)
Decreased appetite	4 (20)
Fatigue	4 (20)
Grade ≥3 TEAEs	11 (55)
Increased GGT	5 (25)
Neutropenia	2 (10)

- Median patient age was 74.5 years (range: 35-93)
- Median number of doses administered: 5 (range: 1-8)
- Median duration of follow-up: 10.8 months (range: 1.9-21.9)
- No new safety signals were demonstrated

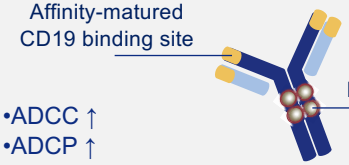
Data cutoff: April 10, 2023

Kwiatek M, et al. SOHO 2023. Abstract ABCL-515

Tafasitamab and Lenalidomide: Rationale for an Immunological Combination



Tafasitamab-cxix (CD19-directed cytolytic mAb)[1–6]



- ADCC ↑
- ADCP ↑
- Direct cell death
- Phase IIa study showed single-agent activity in patients with R/R DLBCL and iNHL

Lenalidomide[4,5]

- T-cell and NK-cell activation/expansion
- Direct cytotoxic and immunomodulatory effects
- Well-studied as an anti-lymphoma agent, alone or in combination

CD19 = cluster of differentiation 19; mAb = monoclonal antibody; Fc = fragment crystallizable; ADCC = antibody-dependent cellular cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; R/R DLBCL = relapsed/refractory diffuse large B-cell lymphoma; iNHL = indolent non-Hodgkin's lymphoma; NK = natural killer.

1. Horton HM, et al. *Cancer Res* 2008;68:8049–57; 2. Woyach JA, et al. *Blood* 2014;124:3553–60; 3 Jurczak W, et al. *Ann Oncol* 2018;29:1266–72; 4. Witzig TE, et al. *Ann Oncol* 2015; 26:1667–77; 5. Czuczman MS, et al. *Clin Cancer Res* 2017; 23:4127–37. 6. MONJUVI Prescribing Information. Boston, MA: MorphoSys US, Inc.

L-MIND Study Rationale

Unmet need in r/r DLBCL

30%–40% of patients with DLBCL fail to respond or show relapse to initial therapy[1]

Patients who fail first-line therapy and are not eligible for HDC/ASCT have a poor outcome and require more therapeutic options[1]

Single-agent activity of Tafasitamab-cxix evaluated in r/r B-cell malignancies

A phase I dose-escalation study in 27 patients with R/R CLL showed the preliminary efficacy of Tafasitamab-cxix[2]

A phase II study of 92 patients demonstrated clinical activity of Tafasitamab-cxix in patients with R/R DLBCL and R/R FL, including those with rituximab-refractory tumors[3]

Lenalidomide may have synergistic effects with Tafasitamab-cxix

Lenalidomide has been well-studied as an anti-lymphoma agent, alone or in combination[4,5]

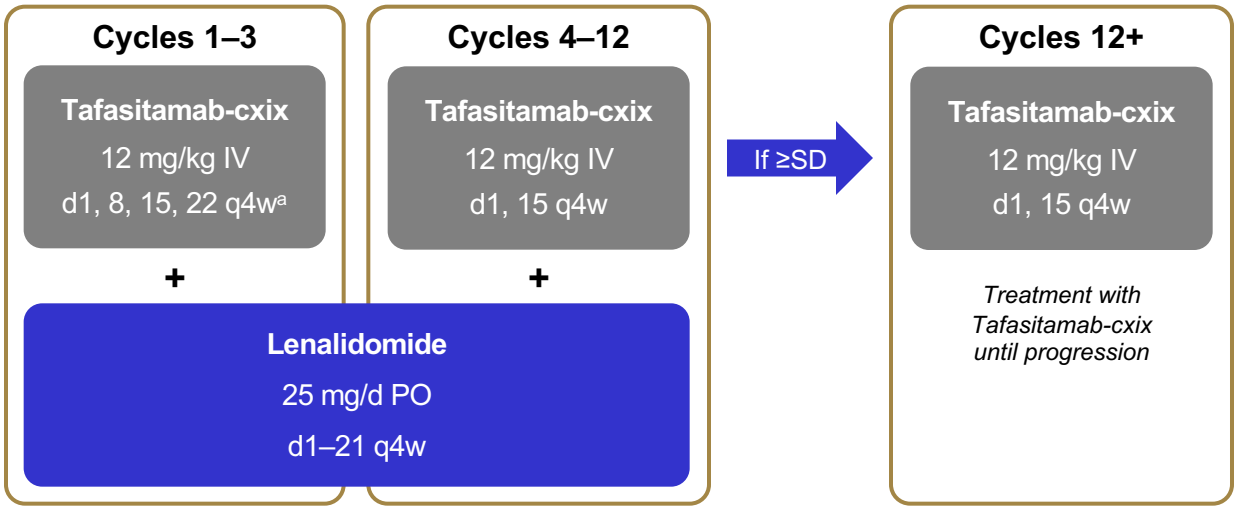
In an *in vitro* study, NK-cell mediated ADCC with Tafasitamab-cxix was further enhanced by lenalidomide[6]

R/R CLL = relapsed/refractory chronic lymphocytic leukemia; R/R FL = relapsed/refractory follicular lymphoma.

1. Crump M, et al. *Blood* 2017;130:1800–8; 2. Woyach JA, et al. *Blood* 2014;124:3553–60; 3 Jurczak W, et al. *Ann Oncol* 2018;29:1266–72; 4. Witzig TE, et al. *Ann Oncol* 2015; 26:1667–77; 5. Czuczman MS, et al. *Clin Cancer Res* 2017;23:4127–37 ; 6. Awan FT, et al. *Blood* 2010;115:1204–13.

Phase II L-MIND Study Design and Inclusion Criteria

- N=81
- Age ≥18 years
- R/R DLBCL
- Not eligible for HDT + ASCT
- 1–3 prior regimens
- Primary refractory patients were excluded[b]
- ECOG 0–2
- ***First Data Analysis: November 2018[1]***
- ***Updated Long Term Outcomes: November 2019[2]***



Primary endpoint:
ORR (ORR = complete response [CR] + partial response [PR])

Select Secondary endpoints:
PFS, DoR, OS, safety, exploratory and biomarker-based assays

[a]Loading dose on day 4 of cycle 1 only.
[b]Primary refractory defined as no response to, or progression/relapse during or within 6 months of front-line therapy.
R/R = relapsed or refractory; IV = intravenous; q4w = every 4 weeks; SD = stable disease; HDT = high dose therapy; ASCT = autologous stem cell transplantation; ECOG = Eastern Cooperative Oncology Group; PO = orally; ORR = overall response rate; PFS = progression-free survival; DoR = duration of response; OS = overall survival.

1. Salles G, Duell J, González Barca E, et al. Tafasitamab-cxix plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol*. 2020 Jun 5;S1470-2045(20)30225-4. doi: 10.1016/S1470-2045(20)30225-4. 2. Salles G, et al. EHA 2020. Abstract EP1201.

L-MIND: Updated Efficacy Outcomes (IRC)

Long term outcomes from L-MIND: Tafasitamab-cxix + Lenalidomide in R/R DLBCL (Phase II)

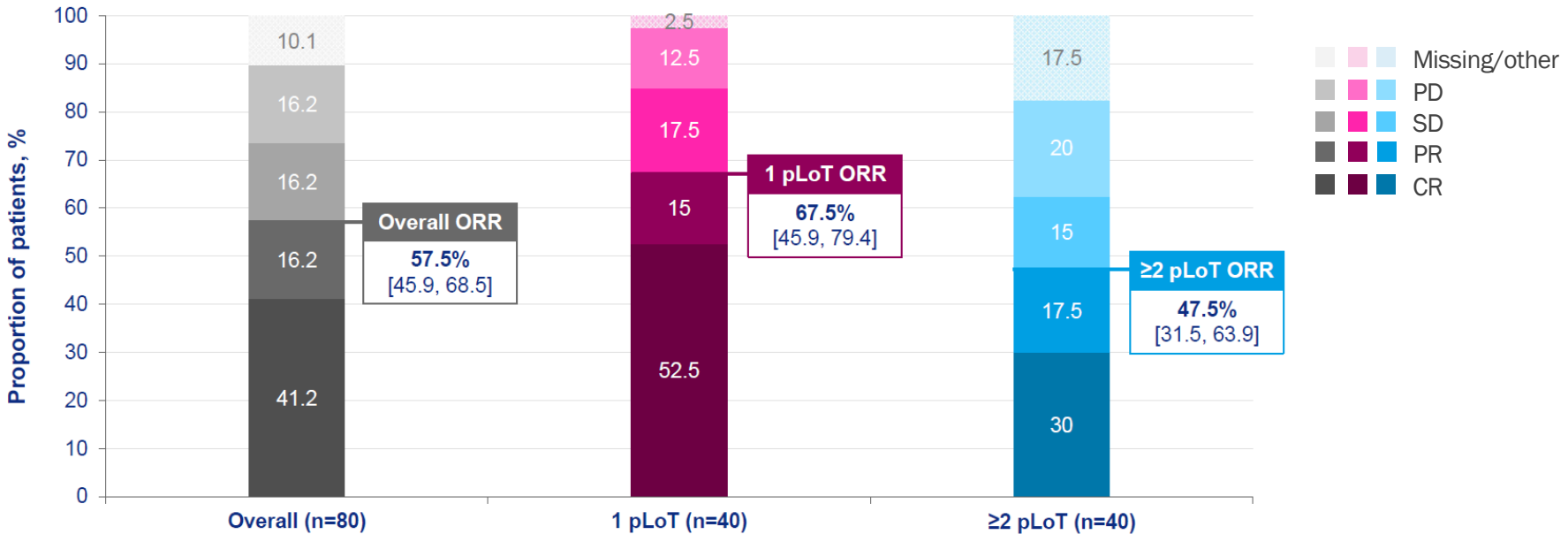
	Nov 2018[1] (n=80)	Nov 2019[3] (n=80)	Nov 2019[3] 2L (n=40)
ORR	60%	57.5%[a]	67.5
CR	42.5%	40.0%[a]	50.0
PR	17.5	17.5	17.5
mDoR	21.7 mo (21.7, NR)	34.6 mo (26.1, NR)	34.6 mo (21.7, NR)
mPFS	12.1 mo (5.7, NR)	12.1 mo (6.3, NR)	23.5 mo (7.4, NR)
mOS	NR (18.3, NR)	31.6 mo (13.8, NR)	NR (24.6, NR)
Patients still on study	N=28	N=22	

The US Prescribing Information(USPI) includes efficacy data on a subset of patients with centrally confirmed diagnoses of DLBCL[2]: N=71; ORR=55%; mDoR=21.7 mo

[a]For 3 patients, additional data accumulating after Nov '18 cut off changed the radiology adjudication within the Independent Review Committee (IRC).
mDoR = median duration of response; mOS = median overall survival.

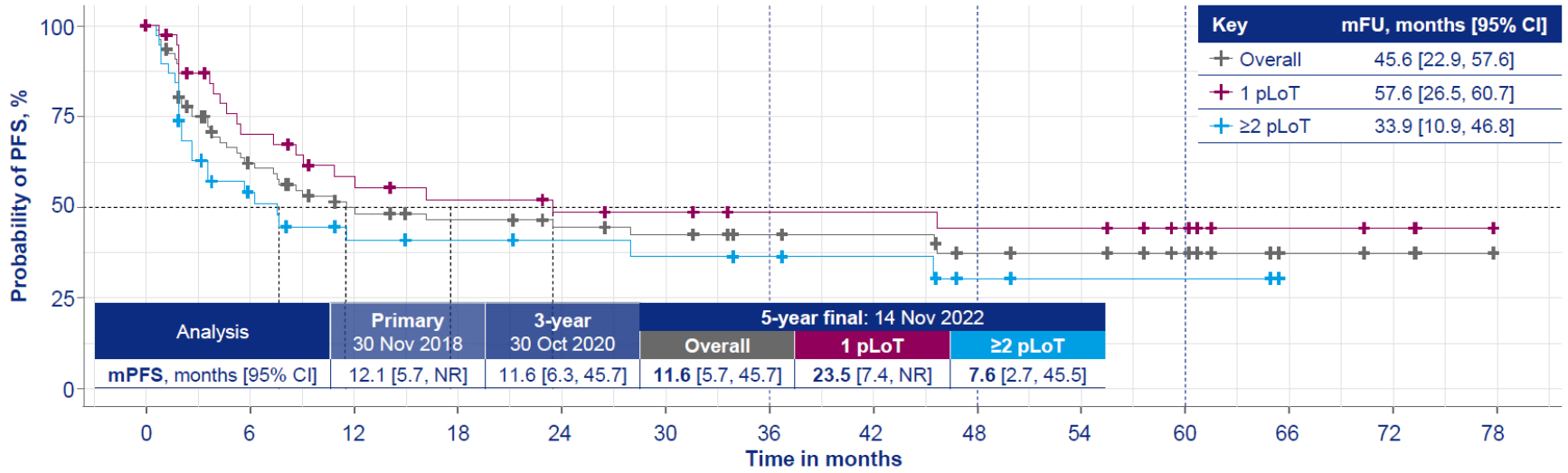
1. Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol*. 2020. 2. MONJUVI Prescribing Information. Boston, MA: MorphoSys US, Inc. 3. Data on File- MOR208C203 EMA Analysis Tables. MorphoSys 2020

L-MIND Final Results: Best Response at 5-Year Follow-Up



Duell J, et al. AACR 2023. Abstract 9810.

L-MIND Final Results: PFS at 5-Year Follow-Up



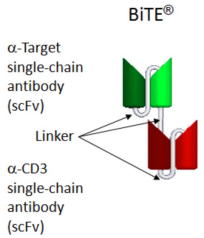
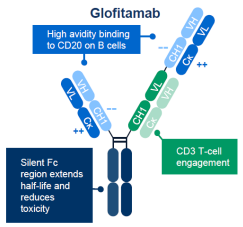
Number at risk:

Overall	80	42	30	26	23	21	18	17	13	12	9	4	3	0
1 pLoT	40	25	19	16	14	13	11	11	10	10	7	4	3	0
≥2 pLoT	40	17	11	10	9	8	7	6	3	2	2	0	0	0

Duell J, et al. AACR 2023. Abstract 9810.

Bispecific AntiBodies

Bispecific Antibodies in Non-Hodgkin Lymphomas

The Original: Proof of Concept	Newer Therapies	
Blinatumomab[1]	Epcoritamab[2]	Glofitamab[3]
		
CD3 (scFV) × CD19 (scFV)	DuoBody- CD3 × CD20 BsAb	CD3 (Fab) × CD20 (Fab x2) Fc BsAb

- Numerous bispecific antibody structures exist
- Properties of the bispecific antibody vary by construct

1. Queudeville M, et al. *Onco Targets Ther*. 2017;10:3567-3578. **2.** Clausen MR, et al. *J Clin Oncol*. 2021;39(Suppl 15):7518. **3.** Hutchings M, et al. *Blood*. 2020;136(Suppl 1):45-46.

Key Bispecific Antibodies in 3L DLBCL: Efficacy and Safety

	Study Phase	Study Population	Clinical Trial	ROA	Sample Size	Median Prior LOT	Efficacy: ORR, CR, mDOR/DoCR	Safety All CRS	Safety Grade ≥3 CRS	Safety Other
Epcoritamab[1,2] [Hospitalization required for 24h after dose on C1 D15]	P1/2	Patients with R/R DLBCL and B-NHL after anti-CD20 treatment	NCT03625037 (EPCORE NHL-1)	SUBQ	DLBCL=46	3 (2-4)	**68%** ORR, **45%** CR (dose 12-60 mg)	59%	0%	Neurological: 6%
					LBCL=157	3 (2-11)	**63.1%** confirmed ORR by IRC, mDOR 12 mo	49.7%	2.5% (Gr 3)	Pyrexia: 23.6% Neutropenia: 21.7%
Glofitamab[4,5] [Pretreatment with obinutuzumab required]	P2	Patients with R/R DLBCL after at least 2 prior systemic therapy	NCT03075696 (NP30179)	IV	DLBCL=155	3 (2-7)	**52%** ORR, **39%** CR	63%	4%	Grade ≥3 NEs: 3%

Epcoritamab and glofitamab have been approved by the FDA for use in R/R DLBCL; mosunetuzumab is not approved by the FDA or other regulatory authorities for use in DLBCL.
This table is for illustration only and side-by-side data should be interpreted with great caution.

1. Hutchings M, et al. *Lancet*. 2021;398(10306):1157-1169. **2.** Thieblemont C, et al. *J Clin Oncol*. 2023;41(12):2238-2247. **3.** Bartlett N, et al. *Blood Adv*. 2023:2022009260. **4.** Dickinson MJ, et al. *N Engl J Med*. 2022;387(24):2220-2231. **5.** Dickinson MJ, et al. ASCO 2022. Abstract 7500.

EPCORE NHL-1 Phase 2 Study of Epcoritamab in Patients with R/R LBCL: Study Design

Dose escalation

Dose expansion data cutoff: January 31, 2022
Median follow-up: 10.7 mo

Key inclusion criteria:

- R/R CD20^{+} mature B-cell neoplasm
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 anti-CD20 mAb
- FDG PET–avid and measurable disease by CT/MRI
- Prior CAR T-cell therapy allowed

Step-up dosing[a]

Epcoritamab SC RP2D 48 mg
QW C1–3,
Q2W C4–9,
Q4W C10+

→ **Treatment until PD[b,c] or unacceptable toxicity**

→ **LBCL Cohort N=157**
DLBCL, HGBCL, PMBCL, and FL Gr3B

- To ensure patient safety and better characterize CRS, inpatient monitoring was required at first full dose for 24 h in this part of the study
- **Primary endpoint:** ORR by independent review committee (IRC)
- **Key secondary endpoints:** DOR, TTR, PFS, OS, CR rate, and safety/tolerability

Data cutoff date: January 31, 2022.
[a]Step-up dosing (priming 0.16 mg and intermediate 0.8 mg dosing before first full dose) and corticosteroid prophylaxis were used to mitigate CRS. [b]Radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter. [c]Measurable disease with CT or MRI scan with involvement of ≥2 lesions/nodes with a long axis >1.5 cm and short axis >1.0 cm (or 1 lesion/node with a long axis >2.0 cm and short axis ≥1.0 cm) and
Thiebelmont, C et al. *J Clin Oncol*. 2023; 41(12):2238-2247.

EPCORE NHL-1 Phase 2 Study of Epcoritamab in Patients with R/R LBCL: Baseline Patient Characteristics

Demographics, n (%)	LBCL N=157
Median age (range), y	64 (20–83)
<65, n (%)	80 (51.0)
65 to <75, n (%)	48 (30.6)
≥75, n (%)	29 (18.5)
ECOG PS, n (%)	
0	74 (47.1)
1	78 (49.7)
2	5 (3.2)
Disease type	
DLBCL	139 (88.5)
De novo	97/139 (69.8)
Transformed	40/139 (28.8)
Unknown	2/139 (1.4)
DHL/THL, n/N (%)	13/99 (13.1)

Prior treatments	LBCL N=157
Median time from initial diagnosis to first dose,[a] y (range)	1.6 (0.0-28.4)
Median prior lines of therapy (range)	3 (2–11)
≥3 Lines of therapy, n (%)	111 (70.7)
Primary refractory[b] disease, n (%)	96 (61.1)
Refractory[b] to last systemic therapy, n (%)	130 (82.8)
Refractory[b] to ≥2 consecutive lines of therapy, n (%)	119 (75.8)
Prior ASCT, n (%)	31 (19.7)
Relapsed within 12 months of prior ASCT, n/N (%)	18/31 (58.1)
Prior CAR T-cell therapy, n (%)	61 (38.9)
Progressed within 6 mo of CAR T-cell therapy, n/N (%)	46/61 (75.4)

Data cutoff date: January 31, 2022.

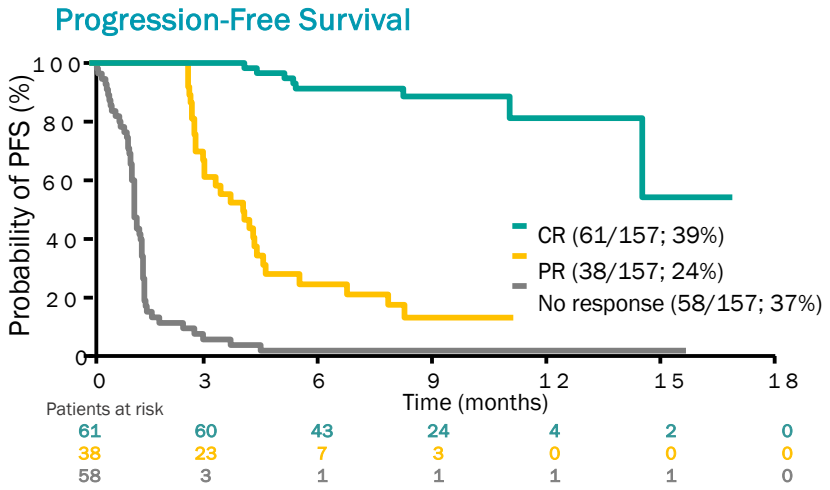
[a]Time from diagnosis of malignancy recorded at study entry. [b]Disease progression or stable disease as best response to therapy or disease progression within 6 months after completion of therapy.

Thiebelmont, C et al. *J Clin Oncol*. 2023; 41(12):2238-2247.

EPCORE NHL-1 Phase 2 Study of Epcoritamab in Patients with R/R LBCL: Overall Response, PFS, and OS[1,2,3]

Best overall response by IRC[a]	LBCL (N=157)
Overall response, n (%) [95% CI]	99 (63.1) [55.0-70.6]
Complete response, n (%) [95% CI]	61 (38.9) [31.2-46.9
Partial response, n (%)	38 (24.2)
Stable disease, n (%)	5 (3.2)
Progressive disease, n (%)	37 (23.6)

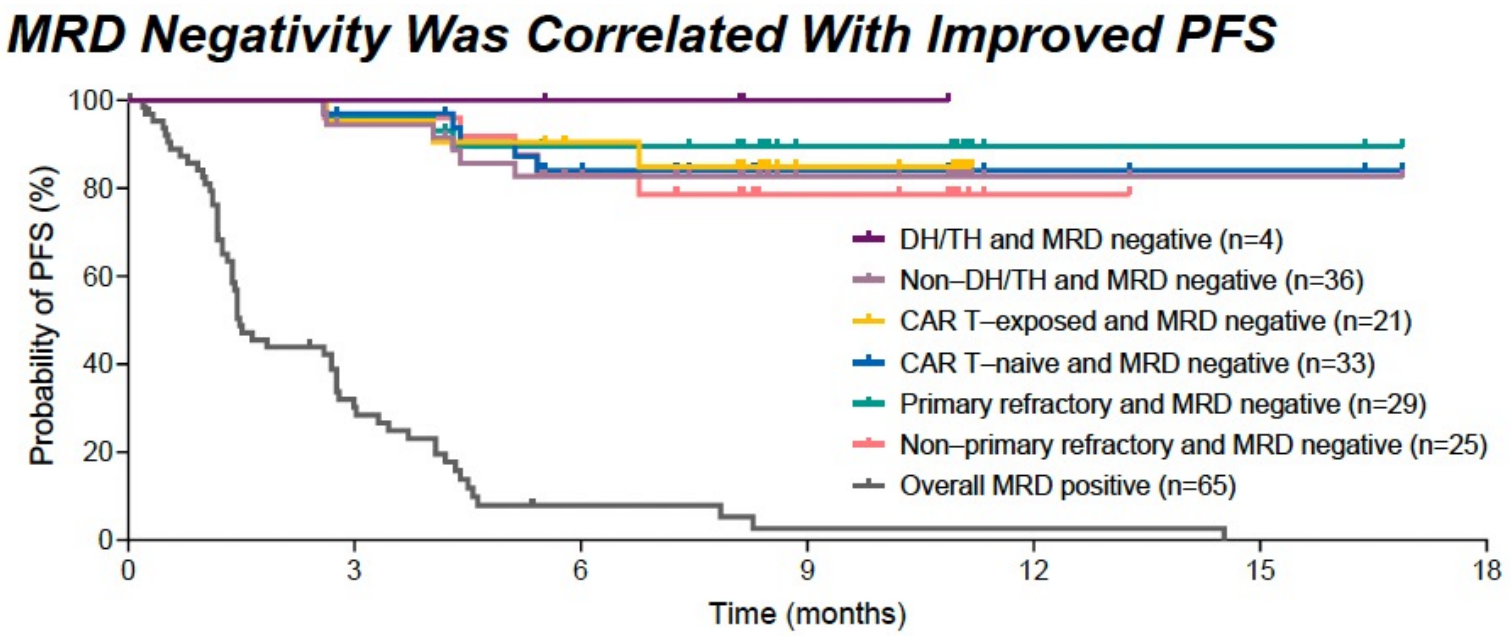
Kaplan-Meier estimate	LBCL (N=157)
Median PFS for complete responders (95% CI)	NR (14.5-NR)
Complete responders remaining in CR at 9 mo, %	88.7
Median PFS, mo (95% CI)	4.4 (3.0-7.9)
PFS at 6 mo, % (95% CI)	43.9 (35.7-51.7)
Median OS, months (95% CI)	18.5 (11.7-NR)
Median OS for patients who achieved a CR (95% CI)	NR (NR-NR)



LB2364. **3.** Jurczak W, et al. EHA 2023. Abstract P1118.

2. Abstract

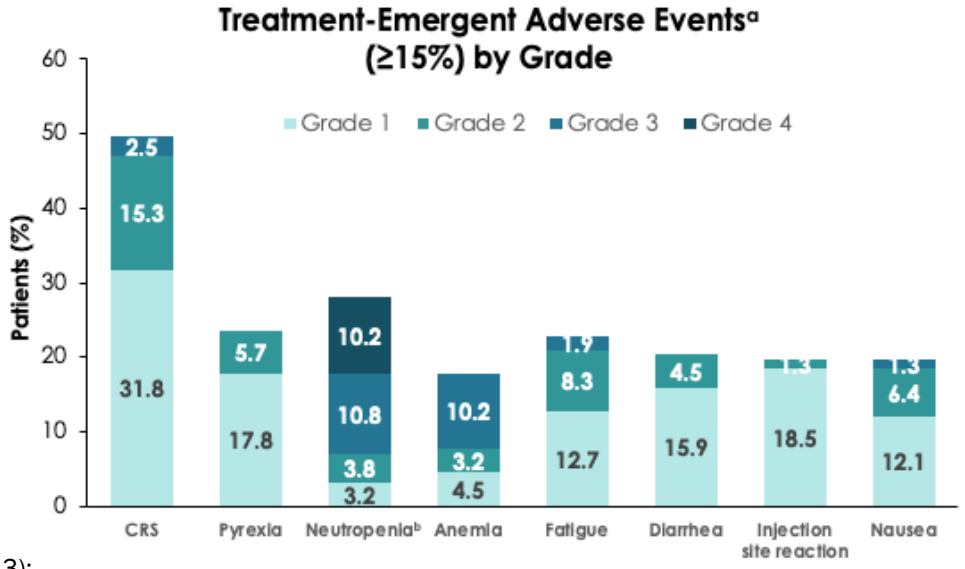
Epcoritamab in R/R DLBCL



Phillips et al, ASH 2022

EPCORE NHL-1 Phase 2 Study of Epcoritamab in Patients with R/R LBCL: Safety

Follow-up	LBCL, N=157
Median follow-up (range), mo	10.7 (0.3–17.9)
Median number of treatment cycles (range)	5 (1–20)
Ongoing treatment, n (%)	51 (32)
Discontinued treatment, n (%)	106 (68)
PD	83 (53)
AE	11 (7)
Related[d]	3 (2)
Allogeneic transplantation	7 (4)
Withdrawal by patient	4 (3)
Other	1 (1)



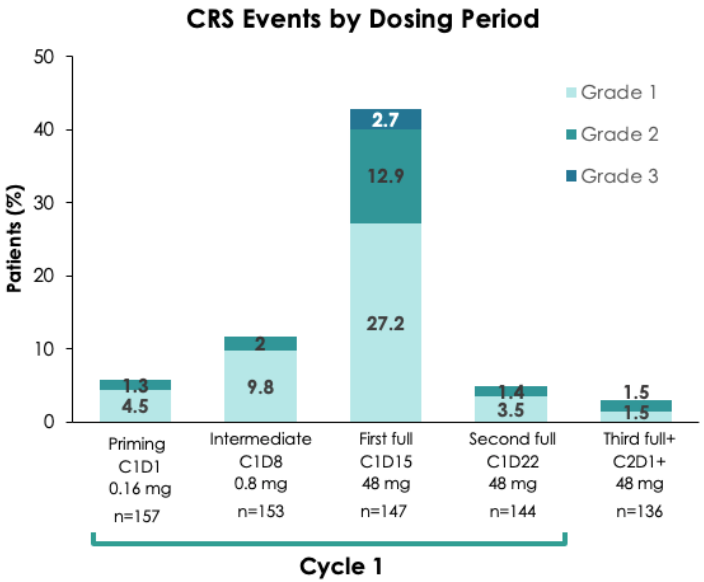
- Most AEs were low grade and occurred early in treatment (C1–3); incidence of AEs declined after 12 weeks
- Ten (6.4%) patients experienced ICANS; 9 were Gr 1/2 and resolved
- 1 patient had ICANS Grade 5, confounded by multiple factors[c]

[a]COVID incidence 4.5%. [b]Combined term includes neutropenia and decreased neutrophil count. [c]Patient experienced ICANS after intermediate dose with multiple confounders, including extensive opioid use for Grade 3 pancreatitis, hyperammonemia, multifocal cerebral infarcts in setting of possible microangiopathy, and tocilizumab administration. [d]Worsening CLIPPERS, CRS/fatigue, and ICANS.

Thieblemont C, et al. EHA 2022. Abstract LB2364.

EPCORE NHL-1 Phase 2 Study of Epcoritamab in Patients with R/R LBCL: CRS Safety

n (%)	LBCL N=157
CRS events[a]	78 (49.7)
Grade 1	50 (31.8)
Grade 2	24 (15.3)
Grade 3	4 (2.5)
Median time to onset from first full dose, d	0.8 (20 h)
CRS resolution	77 (98.7)
Median time to resolution from first full dose, d	2 (48 h)
Treated with tocilizumab	22 (14.0)
Treated with corticosteroids	16 (10.2)
Leading to treatment discontinuation	1 (0.6)



[a]Graded by Lee et al 2019 criteria.

Thieblemont C, et al. EHA 2022. Abstract LB2364.

Phase 2 Study of Glofitamab in Patients with 3L+ R/R DLBCL: Study Design and Patients

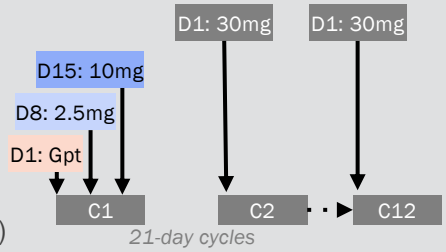
Key Inclusion Criteria:

- DLBCL NOS, HGBCL, transformed FL or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including anti-CD20 antibody and anthracycline

Glofitamab IV Administration:
Fixed-duration treatment (Max 12 Cycles)

CRS mitigation:

- obinutuzumab pretreatment (1 x 1000mg)
- C1 step-up dosing
- monitoring after first dose (2.5mg)



Primary endpoint: CR (best response) rate by IRC[a]
Key secondary endpoints: ORR rate[b], DoR, DoCR[b], PFS, and OS

Baseline Characteristic, n (%)		N=154
Median age, years (range)		66.0 (21–90)
ECOG PS	0	69 (44.8)
	1	84 (54.5)
Ann Arbor stage	I	10 (6.5)
	II	25 (16.2)
	III	31 (20.1)
	IV	85 (55.2)
NHL subtype	DLBCL	110 (71.4)
	trFL	27 (17.5)
	HGBCL	11 (7.1)
	PMBCL	6 (3.9)
Median no. of prior lines, n (range)		3 (2-7)
≥3 prior lines		92 (59.7)
Prior anti-CD20 Ab		154 (100.0)
Prior anthracycline		149 (96.8)
Prior CAR-T		51 (33.1)
Prior ASCT		28 (18.2)
Refractory to any prior therapy		139 (90.3)
Refractory to last prior therapy		132 (85.7)
Primary refractory		90 (58.4)
Refractory to prior CAR-T		46 (29.9)
Refractory to any prior anti-CD20		128 (83.1)

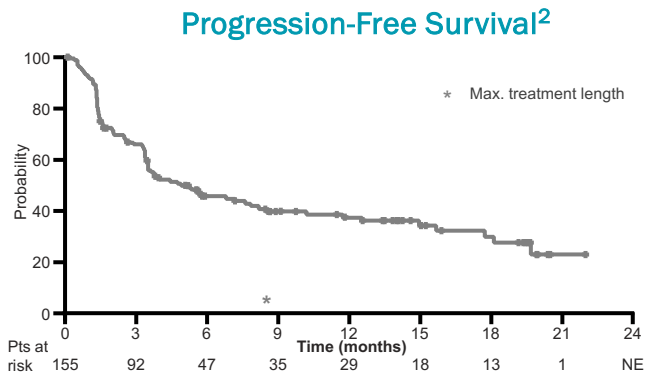
[a]By PET-CT (Lugano critera). [b]By IRC and investigator.
Dickinson M, et al. ASCO 2022. Abstract 7500.

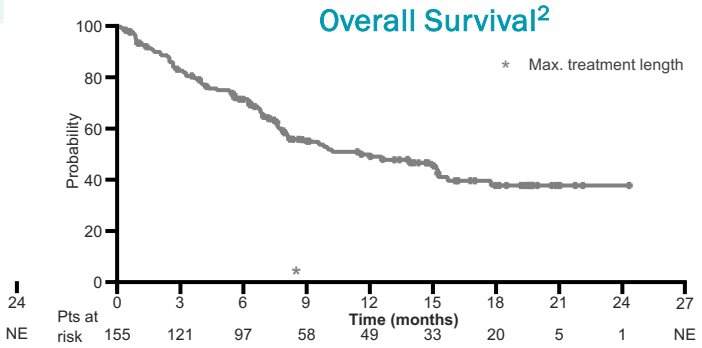
Phase 2 Study of Glofitamab in Patients with 3L+ R/R DLBCL: Efficacy

Efficacy Endpoint[1,2]	Glofitamab 2.5/10/30mg (n=155)
CR rate[a]	61 (39.4%) [95% CI: 31.6%-47.5%]
ORR[a]	80 (51.6%) [95% CI: 43.5%-59.7%]
Median PFS follow-up, mo (range)	12.6 (0–22)
Median PFS, months (95% CI)	4.9 (3.4, 8.1)
Median OS, months (95% CI)	11.5 (7.9, 15.7)

Duration of Overall Response[2]	n=80
Median DoR follow-up, mo (range)	10.6 (0–21)
12-months DoR, % (95% CI)	63.6 (51.1, 76.2)
ORs ongoing at CCOD, n (%)	53 (66.3)

Duration of CR[2]	n=61
Median DoCR follow-up, mo (range)	10.6 (0–21)
12-months DoCR, % (95% CI)	77.6 (64.3, 90.8)
CRs ongoing at CCOD, n (%)	49 (80.3)



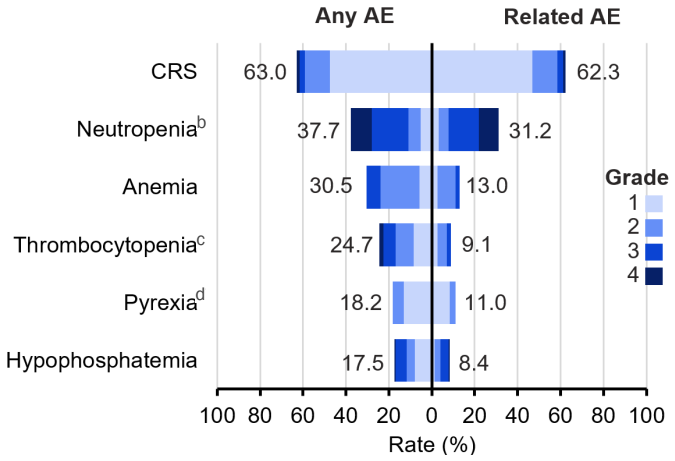


1. Cheson, et al. J Clin Oncol 2014. **2.** Dickinson M, et al. ASCO 2022. Abstract 7500.

Phase 2 Study of Glofitamab in Patients with 3L+ R/R DLBCL: Safety (Cont'd)

Adverse event, n (%)	N=154
Median no. of cycles received (range)	5 (1–13)
Median relative dose intensity, % (range)	100 (94–100)
AE	152 (98.7)
Related AE	140 (90.9)
Grade 3–4 AE	87 (56.5)
Related AE	64 (41.6)
Serious AE	73 (47.4)
Related AE	46 (29.9)
Grade 5 (fatal AE)	8 (5.2)[a]
Related AE	0
AE leading to treatment discontinuation	14 (9.1)
Related AE	5 (3.2)

AEs (≥15%) by grade and relationship with glofitamab



[a]COVID-19/COVID-19 pneumonia (n=5); sepsis (n=2); delirium (n=1). [b]Includes neutrophil count decreased; [c]Includes platelet count decreased. [d]Pyrexia events separate from CRS.

Dickinson M, et al. ASCO 2022. Abstract 7500.

DLBCL
Bottom Line

- Stage I/II-R-CHOP x 3 + IF XRT
  - Vs R-CHOP x 4 w/o XRT (Flyer trial)-low IPI
- Stage III/IV-R-CHOP x 6 vs Pola-CHP
  - Many: Pola-CHP "all comers"-Me: Only in higher risk (high IPI/DEL/ABC)
  - DHL (?DEL)- DA-R-EPOCH + CNS ppx
- Chemo-sensitive relapse (fit < 70)-RICE/R-DHAP/R-Gem-Ox + AutoPSCT
  - Many (R/R w/in 1 yr-CAR T), Me: chemosensitivity counts-ASCT
- Primary Refractory (?) relapse w/in 12 months consider CAR T
- Chemo-insensitive/post-Auto relapse/CAR T failure-consider mini-Allo
- NO SOC for other salvage, But:
  - Consider Tafa/Len 2nd line not ASCT/CAR T candidate
  - Lonca and bispecifics 3rd line
- Always consider clinical trials at *every* step

NCCN Guidelines®: Preferred Treatment Regimens for R/R DLBCL

RECENTLY APPROVED | NOT APPROVED

Patient Segment		Treatment Regimens (NCCN Guidelines® v5.2023)					
1L		R-CHOP	R + Chemo[a]	Pola-R-CHP			
2L	Intention for ASCT	ASCT[b]					
	Relapse <12 mo/primary refractory disease	Axi-cel[c] (Category 1)		Liso-cel[c]			
	Relapse >12 month but ASCT ineligble or relapse <12 month and primary refactory but non-CAR T-cell therapy candidate	CAR T-cell therapy[c] (Liso-cel)	Polatuzumab vedotin ± Bendamustine ± Rituximab (Pola-BR)	Tafa + Len			
		Brentuximab vedotin (CD30+ disease)	Ibrutinib (non-GCB DLBCL)	R + Len (R^2) (non-GCB DLBCL)	Chemo ± R (eg, GemOx ± R)	R	
3L+	≥2 prior regimens	CAR T-cell therapy[c] (Axi-cel, Liso-cel, Tisa-cel)	Loncastuximab tesirine	Selinexor	Glofitamab	Epcoritamab	
	Post-ASCT or CAR T-cell therapy	Selinexor					

[a] Patients with poor left ventricular function, very frail, with comorbidities, or aged >80 years. [b] Salvage chemotherapy ± rituximab precedes ASCT. [c] Bridging chemotherapy precedes CAR T-cell therapy.

NCCN Clinical Practice Guidelines: B-Cell Lymphomas. Version 5.2023.


Questions?